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Current Good Manufacturing Practices and the Federal Food, Drug and Cosmetic Act

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The Food and Drug Administration (hereinafter, FDA) regulates food, drugs, and cosmetics in order to ensure that these products are safe and truthfully labelled. As part of its responsibilities under the Federal Food, Drug, and Cosmetic Act (hereinafter, Act), the FDA monitors the manufacturing practices of companies involved in the production of food, drugs, and medical devices. The manufacturing practices used by these companies must comply with certain standards, identified in the Act as current good manufacturing practices (hereinafter, CGMP). If a company's practices do not conform with CGMPs, the finished products are considered adulterated, even if the products are technically perfect. The purpose of CGMPs is to assure the safety and efficacy of the finished products.

CGMP represents a process-oriented regulation—a regulation which focuses on the technology and/or practices used in production, rather than on the output. By managing the process, the regulatory agency can also control the quality and impacts of the completed product. This paper reviews the basic aspects of the CGMP requirement and considers whether government agencies should be involved in regulating the process as well as the final product. In addressing the process-product distinction, the paper compares the CGMP regulations to a similar process-oriented regulation found in the Clean Air Act—the requirement that certain permitted facilities use the best available control tech-

nology. Basic Features of CGMP

The requirement that manufacturers comply with current good manufacturing practices originates in the Federal Food, Drug and Cosmetic Act. The Act specifically mentions conformity with CGMP only in relation to medical drugs and devices.¹ Section

501(a)(2)(B) of the Act requires the methods, facilities, and controls used in the manufacture, processing, packing and holding of a drug product to conform to current good manufacturing practice in order to assure that the drug meets the safety requirements of the Act and that the drug has the identity, strength, quality, and purity which it purports to possess. Section 520(f)(1)(A) authorizes the Secretary of Health, Education and Welfare to prescribe regulations requiring conformity with CGMP in the manufacture, pre-production design validation, packing, storage, and installation of medical devices.² The Act does not specifically mention CGMP in relation to the production of food. In order to promulgate CGMP regulations for food production, the FDA relies upon statutory authority which deems food to be adulterated if it consists of any filthy, putrid, or decomposed substance or if it has been prepared, packed, or held under insanitary conditions where it may have become contaminated with filth.³ The regulations establish the practices a food manufacturer should

¹Federal Food, Drug, and Cosmetic Act §501(a)(2)(B), 21 U.S.C. §351 (1988 & Supp. V) (requiring compliance with CGMP in the manufacture of drugs); Federal Food, Drug, and Cosmetic Act §520(f)(1)(A), 21 U.S.C. §360(j)(t) (1988 & Supp. V) (permitting the promulgation of regulations for COMP related to the manufacture of medical devices).

²Section 501(a)(2)(B) of the Act does not provide the Secretary with the authority to promulgate CGMP regulations relating to the manufacture of drugs. The Secretary derives the authority from Section 701 of the Act, which gives the Secretary the authority to prescribe regulations for the efficient enforcement of the Act. Federal Food, Drug, and Cosmetic Act §701(a), 21 U.S.C. §371(a) (1988 & Supp. V).

³Federal Food, Drug, and Cosmetic Act §402(a)(3), (4), 21 U.S.C. §342 (1988 & Supp. V).

follow in order to avoid violating this section of the Act.⁴

By regulating the manufacturing practices of food and drug producers, the FDA places emphasis on the process, as well as the final product. As explained in the statute and the corresponding regulations, the purpose of requiring conformity with CGMPs is to assure the safety and efficacy of the product.⁵ With drug products, CGMPs are also designed to ensure the drug has the identity and strength, and meets the quality and purity characteristics, which it purports to possess. Following the CGMP regulations does not guarantee that a properly manufactured product will not be adulterated; [d]efects can creep into a finished product in spite of the most careful adherence to any kind of GMPs.⁶ Likewise, approval of the selected manufacturing standards and procedures outlined in a new drug application (NDA) or an abbreviated new drug application (ANDA) does not shield a company from FDA action if the process generates failures to comply with CGMP regulations. In *United States v. Barr Laboratories, inc.*, the court determined that an ANDA guides a product's manufacture and release, but does not supersede the overarching CGMP requirements.⁷ However, CGMPs can guide manufacturers to the establishment of reasonable practices and procedures that are capable of reproduction and which *reduce* the possibility of a process which will lead to or allow the production of an adulterated product.⁸ The CGMP requirement allows FDA to

⁴Stephen H. McNamara, *Preparing for Cosmetic GMP—A Legal Perspective*, 35 Food Drug Cosm. L.J. 651, 654-655 (1980).

⁵*E.g.*, 21 U.S.C. §§ 351, 360(j) (1988 & Supp. V); 21 C.F.R. §210.1(a) (1994).

⁶Patrick V. Gibbons, *Legal Implications of GMP Regulations*. 31 Food Drug Cosm. L.J. 473, 475 (1976).

⁷*Barr Laboratories*, 812 F.Supp. at 465.

⁸Christopher L. Hagenbush, *How the FDA and Industry Use Guidelines in Defining and*

monitor operations and correct faulty manufacturing processes before defective products are completed.⁹

FDA must also monitor the manufacturing process to ensure that a company does not violate the legal definition of adulterated. Under Section 501(a)(2)(B) of the Act, a pharmaceutically-perfect drug is considered to be adulterated if the manufacturer did not comply with the CGMP regulations during production.¹⁰ By including the requirement of compliance with CGMP in the statute and by promulgating CGMP regulations to guide manufacturers, Congress and the FDA underscore the important connection between the quality of the process and the quality of the finished product.

Regulations and Guidelines

The CGMP requirement established in the Federal Food, Drug, and Cosmetic Act provides only a general standard against which firms can measure their manufacturing processes. Several courts, however, have found that the drug GMP requirement is not unconstitutionally vague. According to the courts, CGMP is a term of art directed at a particular group, who can be expected to know the actions and procedures necessary to comply with the standard.¹¹ In addition, FDA provides more specific guidance through regulations

Interpreting Statutory Requirements, 38 Food Drug and Cosm. L.J. 177, 181 (1983) (emphasis added).

⁹Seymour B. Jeffries, *Current Good Manufacturing Practices Compliance—A Review of the Problems and an Approach to Their Management*, 23 Food Drug Cosm. L.J. 580 (1968).

¹⁰*E.g.*, United States v. Barr Laboratories, Inc., 812 F.Supp. 458, 486 (D.N.J. 1993) (citing United States v. Lit. Drug Co., 333 F.Supp. 990, 998 (D.N.J. 1971)) (indicating the relevant inquiry in determining whether a drug is adulterated focuses on the legal definition, not on the pharmaceutical perfection of the drug); Gibbons, *supra* note 6, at 475.

¹¹McNamara, *supra* note 4, at 653 (citing United States v. An Article of Drug.. White Quadriseet. 484 F.2d 748 (CA-7, 1973), United States v. Kendall Co., 324 F.Supp. 628 (D.C. Mass. 1971), United States v. Bel-Mar Laboratories, Inc., 284 F.Supp. 875 (D.C. E.D. N.Y. 1968)).

and guidelines, assisting companies in determining the type of manufacturing practices which qualify as current and good.

Promulgated by the FDA through the Code of Federal Regulations, CGMP regulations establish the minimum practices necessary for a manufacturer to conform to the statutory requirement.¹² The regulations outline general rules for all aspects of [food and] drug manufacture, including buildings and facilities, personnel, equipment, drug components and containers, production, packaging and labeling, and record-keeping.¹³ In the CGMP regulations, FDA addresses, among other topics, equipment design, size and location; batch production and control records; and personnel habits and responsibilities. In one sense, the regulations are very specific, requiring personnel engaged in any aspect of the manufacturing process to wear clean clothing appropriate for their duties and practice good sanitation.¹⁴ On the other hand, the regulations do not provide guidance as to what qualifies as good sanitation and health habits. Often the regulations will use the term adequate, without relating how the term can be satisfied. For example, section 211.22(b) requires adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products... but there is no explanation indicating what features make a laboratory adequate.¹⁵ Because the regulations are often very broad and vague, they allow conflicting, but plausible, views of the requirement; this, in turn, transform[s]

¹²21 C.F.R. §210.1(a) (1994); *Barr Laboratories*, 812 F.Supp. at 465.

¹³*Barr Laboratories*, 812 F.Supp. at 465.

¹⁴21 C.F.R. §211.28(a), (b) (1994).

¹⁵21 C.F.R. §211.22(b) (1994).

what might be a routine evaluation into an arduous task.¹⁶ While offering significantly more guidance than the statute, the CGMP regulations leave room for subjective interpretation and allow arbitrary action by FDA inspectors.

In the *Barr Laboratories* decision, the court suggests that, when the CGMP regulations create ambiguities, industry can obtain further guidance from seminar and pharmaceutical firm literature, textbooks, reference books, and FDA letters to manufacturers.¹⁷ Companies cannot use industry standards alone to settle questions of CGMP compliance, however. According to the *Barr Laboratories* court, industry standards themselves must be reasonable and consistent with the spirit and intent of the CGMP regulations.¹⁸ In addition to these other sources, companies can rely upon FDA guidelines addressing CGMP compliance.

FDA guidelines act as an advisory opinion directed generally to the behavior of all those engaged in a certain type of activity and represent the agency's best judgement standards.¹⁹ Unlike regulations, FDA guidelines are not binding on industry; companies may follow the guidelines or they may choose other, perhaps more innovative, methods.²⁰ In addition, guidelines offer greater flexibility to FDA because FDA can provide advice to industry without establishing an enforcement program.²¹ Guidelines can be adapted more quickly than regulations and therefore can reflect changing technology and business

¹⁶ *Barr Laboratories*, 812 F.Supp. at 465.

¹⁷ *Barr Laboratories*, 812 F.Supp. at 465.

¹⁸ *Id.*

¹⁹ Hagenbush, *supra* note 8, at 178.

²⁰ *Id.* at 178-179.

²¹ *Id.* at 179.

practices.²²

In practice, guidelines do not offer the same flexibility suggested in theory. FDA inspectors are often suspicious of processes which differ from those established in a guideline, giving the guideline the same binding effect as the statute or regulations.²³ FDA may also draft a guideline using language such that following the recommendations in the guideline represents the only reliable method for achieving compliance.²⁴ In his article, Christopher Hagenbush uses the example of FDA's draft process validation guidelines issued to interpret the CGMP requirement for drugs.²⁵ The draft guidelines establish the need for three qualification runs on equipment, a suggestion which represents FDA's opinion as to the number of repetitions necessary to establish fitness of the equipment. Hagenbush suggests a company would have a difficult time justifying fewer than three qualification runs, especially since a court would probably defer to FDA's judgment.²⁶ Because the guidelines represent FDA's expert opinion, companies may have a difficult time substituting a different procedure for complying with COMP requirements, even if the company's process is more procedure for complying with CGMP requirements, even if the company's process is more reasonable or more innovative. A company wishing to use a different procedure must defend its requirement against the FDA guideline. Many companies may not wish to undertake this task, particularly if there is deference to FDA's opinion.

²² *Id.*

²³ *Id.* at 178.

²⁴ *Id.* at 180.

²⁵ *Id.* (citing 48 Fed. Reg. 13,096 (March 29, 1983)).

²⁶ *Id.*

Process versus product regulation

As mentioned earlier, CGMP requirements focus regulatory efforts on the manufacturing process rather than the finished product. CGMP requirements force FDA personnel, particularly the inspectors, to be familiar with manufacturing technology and practices as well the specifications with which the final product (food or drug) must comply. For instance, an FDA inspector must know enough about manufacturing practices to determine if equipment has the appropriate design and adequate size, as well as being suitably located.²⁷ A similar process-oriented requirement in the Clean Air Act—the mandatory inclusion of the best available control technology (hereinafter, BACT) in the permit for a major source or modification—shifts the attention of permit writers at the Environmental Protection Agency (hereinafter, EPA) from emissions limits to the technology for achieving those limits.²⁸ The requirement that each permit identify the best available control technology, to be employed at the permitted facility, forces permit writers to become familiar with technologies used for pollution control. In addition, permit writers must be able to determine when a technology does not qualify as BACT for a particular facility.²⁹ Without these

²⁷21 C.F.R. §211.63 (1994).

²⁸Each permit issued under the nondegradation program, also known as the Prevention of Significant Deterioration (PSD), must include emission limits, an analysis of air quality impacts, and the imposition of BACT. Clean Air Act §165(a), 42 U.S.C. §7475(a). The Clean Air Act defines BACT as an emission limitation based on the maximum degree of reduction of each regulated pollutant that can be achieved considering the energy, environmental, and economic impacts and other costs associated with the application of production processes or available methods, systems and techniques. Clean Air Act § 169(3), 42 U.S.C. §7479.

²⁹BACT is determined on a case-by-case basis. In analyzing control technologies to determine BACT for a facility, the permit applicant must use a top-down approach which requires the ranking of all available control devices in descending order of effectiveness. An applicant must use the most stringent requirement as BACT, unless the applicant can prove, to the satisfaction of the permitting authority, that technical considerations or energy, environmental, or economic impacts make the use of the top-ranked technology infeasible. Once BACT is established, the reviewing authority specifies an emissions limitation for the source that re-

process-oriented requirements, regulators would focus solely on the output of the facilities: FDA inspectors would determine the safety and efficacy of finished foods and drugs, while EPA permit writers would concentrate on identifying appropriate emissions limits. The manufacturers and the polluting facilities would be responsible for determining the most effective methods for achieving the final, regulated product. Since the Federal Food, Drug, and Cosmetic Act and the Clean Air Act already include these process-oriented regulations, the question becomes: should the FDA and EPA be involved in regulating the process as well as the product?

In both pollution control and the manufacture of food and drugs, the outcome is strongly linked to the process, making government regulation of the process as well as the product important. With BACT, the reviewing agency establishes the emission limit for a facility based on the choice of a particular control technology. Each control technology can achieve certain emission reductions, but each one also results in environmental, energy, and economic impacts. The emission reduction capabilities are balanced against the possible impacts in the selection of BACT. Because the reviewing authority sets the emission limits for a facility based on the choice of a particular control technology, it is important for the EPA to have the authority to be involved in the process of pollution control—by mandating the use of a specific technology—as well as in the regulation of the output.

flects the maximum degree of reduction achievable for each regulated pollutant. Office of Air Quality, Environmental Protection Agency, New Source Review Workshop Manual: Prevention of Significant Deterioration and Nonattainment Area Permitting (Draft) (October 1990) [hereinafter, NSR Workshop Manual].

Similar arguments can be made in defense of FDA authority to establish CGMP for the manufacture of food and drug products. Good manufacturing practices are particularly important when dealing with emerging technologies and new products. For instance, with recombinant DNA and hybridoma technology, there may be changes in potency or mutations during the manufacturing process which can result in unintended and potentially dangerous alterations of the product.³⁰ In such cases, it is necessary to regulate the manufacturing practices in order to ensure the safety and efficacy of the finished product. In addition, monitoring adherence to CGMPs can be important in the manufacture of new products, which often involve new production operations, advanced technologies, and modified designs.³¹ Often, in the approval of applications for new products, safety and efficacy decisions are based upon... specifications contained in the applications. Adherence to GMPs ensures that these specifications will be met consistently from one production run to another.³² Because the quality of the product is often tied to the practices employed in its manufacture, regulation of the process, as well as monitoring the final product, enables FDA to fulfill its function of protecting public health by ensuring the safety and efficacy of products. FDA regulation of manufacturing practices also deters substandard operators who cut corners and gamble with careless operations which pose serious hazards to public health.³³

³⁰Stuart L. Nightingale, *Emerging Technologies and FDA Policy Formulation: The impact of Government Regulation on Developing Drugs from New Technologies*, 37 Food Drug Cosm. L.J. 212, 220 (1982).

³¹Ronald M. Johnson, *GMPs and the Product Review Process*, 48 Food Drug Cosm. L.i. 299 (1993).

³²*Id.*

³³Roscoe P. Kandle, *Application of Current Good Manufacturing Practices*, 24 Food Drug

Despite the benefits gained by linking regulation of the process and product, there are some substantial drawbacks to having the EPA and FDA involved in decisions affecting technology choices and manufacturing practices. First, in order to properly evaluate control technologies and manufacturing practices, government personnel must be kept up-to-date with new developments and innovations in the appropriate fields. This requires a significant investment in the training and education of EPA and FDA personnel, as well as drawing resources and attention away from other agency functions. In addition, both the BACT and the CGMP requirements may impact innovation by private industry.³⁴ Under the BACT requirement in the Clean Air Act, the permit specifies the type of control technology to be used at a particular facility. The operator must obtain a new permit if it wishes to make modifications to the facility, including the use of a different control technology. It may also be difficult to have an innovative technology approved as BACT during the initial permitting process. The operator ranks the available control technologies according to their control effectiveness,³⁵ and the top-ranked alternative must be selected as BACT, unless the applicant can demonstrate significant or unusual impacts caused by the use of that technology at the facility. Therefore, if the innovative technology is not ranked at the top of the list, it is unlikely that the technology will be accepted as BACT. Private industry might be reluctant to invest in the development of new control technologies due to the rigid selection process

Cosm. L.J. 9 (1969).

³⁴But see Nightingale, *supra* note 30, at 220-221 (concluding that FDA regulation does not impede innovation).

³⁵N5R Workshop Manual, *supra* note 29, at B.22.

and the lack of certainty that the technology could be employed by permitted facilities.

The same uncertainties and limitations on flexibility appear when dealing with manufacturing processes regulated by the Federal Food, Drug, and Cosmetic Act. The

CGMP regulations offer little incentive for innovation in manufacturing practices since not even prior approval of the selected standards and practices through the NDA or ANDA guarantees compliance with CGMP. Furthermore, as discussed above, the standards established in FDA regulations and guidelines often become fixed, forcing manufacturers to follow FDA's procedures or justify their alternative practices. Although CGMPs are designed as minimum standards, there is no guarantee that innovative practices will meet or exceed these minimums; a manufacturer using an innovative procedure faces the possibility of non-compliance with CGMP regulations. Since there are no incentives for innovation, it is unlikely that manufacturers will take the initiative and vary their practices from accepted CGMPs.

In order to counteract the inflexibility currently associated with CGMP regulations and guidelines, the FDA could focus on the general principles to be achieved through monitoring manufacturing practices, rather than on the minor details which do not affect the quality efficacy or safety of a product.

³⁶ A 1978 Federal Register notice discussed goal-oriented versus how to GMP requirements. Goal-oriented GMPs would focus on what needs to be achieved

³⁶Irwin S. Shupe. *GMPs ó An Industry Point of View*, 24 Food Drug Cosm. L.J. 14 (1969).

and would provide flexibility in how the requirement is met.³⁷ Irwin Shupe, writing as the Director of Quality Control at Winthrop Laboratories, echoed similar sentiments. In his article, Mr. Shupe argues for emphasizing basic principles of quality control rather than restrictive details; he suggests that specific CGMP regulations can stifle progress and lead to mediocrity.³⁸ Less specific CGMP regulations would encourage innovation and provide flexibility for companies in developing manufacturing practices. However, general regulations do not provide sufficient guidance in complying with CGMP requirements, and they give greater discretion to FDA in enforcing the regulations. In addressing the specificity of guidelines, both industry and FDA face a dilemma: general guidelines permit arbitrary action by FDA, while specific guidelines limit industry flexibility and stifle innovation.

Conclusion

Process-oriented regulations present several drawbacks, including restricting flexibility and innovation by private industry. However, process-oriented regulation serves as a valuable and important addition to product-oriented regulation. By controlling the process, the agency has more confidence in the outcome. In addition, because of the impacts generated by the process, it may be necessary for the relevant agencies to control the process as well as the finished product. With the BACT regulations, EPA authority over the selection of technology ensures that all environmental, energy, and economic impacts of the choice are considered. Under the CGMP regulations, FDA can control the

³⁷McNainara, *supra* note 4, at 660 (citing 43 Fed. Reg. 45,015 (1978)).

³⁸Shupe, *supra* note?, at 16.

manufacturing practices to ensure that the process results in safe and effective products, fit for human use. The best way to negotiate between the benefits of government control over the process and the desire for greater flexibility and innovation may be to allow greater involvement by industry in developing and implementing process-oriented regulations.